Inhibition of TGF-β1 signaling restores both microenvironmental and stem cells abnormalities in the Gata-1low Mouse Model of Myelofibrosis

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Primary myelofibrosis (PMF) is characterized by abnormal megakaryocyte (Mk) development, fibrosis and ineffective hematopoiesis in the marrow and hematopoiesis in extramedullary sites [1]. Studies in animal models have suggested that fibrosis is established by fibroblasts activated by TGF-β1 released by the abnormal Mk. Increased levels of TGF-β1 expression in Mk have been implicated in the development of PMF. To clarify whether TGF-β1 alterations are involved in the development of PMF in Gata1low mice, the TGF-β1 content of Mk from the marrow and spleen from PMF patients and Gata1low mice was compared, the TGF-β1 pathway of the marrow and spleen of the Gata1low mouse PMF model was profiled and the consequences of pharmacological inhibition of TGF-β1 signaling, obtained through treatment with SB431542, was determined. Bone marrow (BM) sections from PMF patients contain 4-times more Mk than those from normal donors and great numbers of Mk are also detectable in their spleen. In addition, Mk from both BM and spleen of PMF patients reacted 34-times more intensely than normal Mk with the TGF-β1 antibody. Similarly the number of Mk in BM and spleen of Gata1low mice was 2-3-fold greater than normal and these cells reacted 3-8-times more intensely with the TGF-β1 antibody than wild-type(wt)Mk. These results were confirmed by immunoelectron-microscopy. On average, one Mk from wild-type and Gata1low mice contained 10.3±2.2 and 54.3±6.5 immunogold-particles per area (p<0.01). SB431542-treatment reduced the intensity of TGF-β1 staining of Gata1low Mk both in BM (5.3±1.1) and spleen (9.2±0.7) compared to Mk both in BM (18.9±0.8) and spleen (24.3±0.9) of Gata1low vehicle-treated mice, while had modest effects on the expression of VEGF and CXCL12. Inhibition of TGF-β1 signaling activates hematopoiesis in BM while reducing extramedullary hematopoiesis in spleen of Gata-1low mice. In addition, it reduced fibrosis, vessel microdensity, increases Ptl counts and decreases WBC and poikilocytes in the blood of Gata1low mice suggesting a potential benefit for treatments targeting microenvironment abnormalities in PMF.

References

Keywords: Myelofibrosis, megakaryocytes, TGF-β1, hematopoiesis.